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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,844	02/03/2006	Tatsuo Hoshino	21425 US C038435/0185658	2034

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EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	
ART UNIT	**PAPER NUMBER**
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,844	HOSHINO ET AL.	
	Examiner	Art Unit	
	Iqbal H. Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-3 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-3 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 03/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 of PCT/EP03/10684.

Claims 1-3 are pending and are present for examination.

Priority

Acknowledgement is made of applicants claim for foreign priority of EP 02021641.2 of 9/27/2002. However, the current claims have not been granted the benefit of the claimed priority date because there is no support for the claimed invention in the provisional application.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 3/23/2005 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

There is no drawing with this application.

Claim Objections

Claims 1 and 2 are objected to because of the following informalities: "conductive" should be "conducive". Appropriate correction is required.

Claim 1 is objected to because of the following informalities: replace "that encodes" with "encoding". Appropriate correction is required.

Claim 1, part (d) is objected to because of the following informalities: replace "which codes for" with "encoding". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is indefinite in the recitation "to the extent of at least 80%" which is ambiguous and confusing. It is unclear whether applicant meant "at least 80%" or something else. However, the examiner would interpret the phrase as "at least 80%. Accordingly, claims 2 and 3 are rejected as they depend on claim 1. "Clarification is required.

Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the present instance, claim 1 recites the ""hybridizes under standard conditions", but the specification does not define what conditions constitute "standard". While page 3 attempt to describe a standard condition, the description is merely exemplary and not a clear definition. In the art the meaning of the term "standard" varies widely depending on the individual situation and the person making the determination. Accordingly, claims 2 and 3 are rejected as they dependent on claim 1. "Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for the biological production of vitamin B6 comprising cultivating a Sinorhizobium cell transformed or transfected by a DNA molecule of SEQ ID NO: 1 from S. meliloti encoding a polypeptide of SEQ ID NO: 2 having D-erythronate-4-phosphate dehydrogenase activity, does not reasonably provide enablement for a process for the biological production of vitamin B6 comprising cultivating any host cell transformed or transfected by any DNA molecule or a fragment thereof, encoding any polypeptide having D-erythronate-4-phosphate dehydrogenase activity or any DNA molecule, which is 80% identical to SEQ ID NO: 1 encoding any polypeptide which is 80% identical to SEQ ID NO: 2 having flavin adenine dinucleotide-dependent D-erythronate 4-phosphate dehydrogenase activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1 and 2 are so broad as to encompass a process for the biological production of vitamin B6 comprising cultivating any host cell transformed or transfected by any DNA molecule or a fragment thereof, or any DNA molecule, which is 80% identical to SEQ ID NO: 1 encoding any polypeptide which is 80% identical to SEQ ID NO: 2 having flavin adenine dinucleotide-dependent D-erythronate 4-phosphate dehydrogenase activity. Claim 1 also recites any DNA molecule, which hybridizes under any standard conditions to the DNA sequence complementary to the DNA sequence of SEQ ID NO: 1 or a fragment thereof. Claim 2 recites the process for the biological production of vitamin B6 which comprises introducing said DNA

molecule into an appropriate host cell, cultivating the obtained host cell under the condition conducive to the production of vitamin B6, and recovering vitamin B6 from the culture and claim 3 recites the process, wherein said host cell belongs to the genus Sinorhizobium.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of DNA molecules encoding any polypeptide having D-erythronate-4-phosphate dehydrogenase activity broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only one polypeptide having D-erythronate 4-phosphate dehydrogenase activity.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple point mutations or substitutions.

The specification does not support the broad scope of the claims which encompass any

DNA molecule or a fragment thereof, or any DNA molecule having 80% sequence identity to SEQ ID NO: 1 because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting D-erythronate 4-phosphate dehydrogenase activity; (B) the general tolerance of D-erythronate 4-phosphate dehydrogenase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any D-erythronate 4-phosphate dehydrogenase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any DNA molecule or a fragment thereof, or any DNA molecule having 80% sequence identity to SEQ ID NO: 1. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any DNA molecule or a fragment thereof, or any DNA molecule having 80% sequence identity to SEQ ID NO: 1 having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2 are rejected under 35 U.S.C. 103 (a) as being obvious over Capela et al. (UniProt Accession No. Q92RK3, Putative oxidoreductase protein, created 12/1/2001, see IDS), Capela et al. (Analysis of the chromosome sequence of the legume symbiont Sinorhizobium meliloti strain 1021, Proc Natl Acad Sci U S A. 2001 Aug 14; 98(17): 9877-82. Epub 2001 Jul 31, see IDS) in view of Yocum et al. (US PGPUB 2005/0164335 A1, publication 7/28/2005, claim priority of 60/367,863 of 3/25/2002 and 60/368,618 of 3/29/2002). Capela et al. (UniProt) teach a putative oxidoreductase protein, which is 100% identical to SEQ ID NO: 2 of the instant application, inherently a erythronate4-phosphate dehydrogenase and the corresponding nucleotide sequence (SMc00985 gene, PNAS 2001), which is 100% identical to the nucleic acid sequence of SEQ ID NO: 1 of the instant application. Capela et al. do not teach a process for producing vitamin B6.

However, Yocum et al. teach a process for producing pyridoxal or pyridoxine or vitamin B6 comprising a host cell, wherein host cell is E. coli, comprising a PdxB gene (pyridoxine or

vitamin B6 biosynthetic gene), which is very similar to PdxR gene of instant application. Yocum et al. also teach cloning the gene in a vector, transforming E. coli as host cell and culturing the recombinant host cell, producing vitamin B6 and recovering from the culture. Yocum et al. do not teach use of PdxR gene from Sinorhizobium meliloti.

It has long been known that Sinorhizobium meliloti is an over-producer of vitamin B6 (constitutively). Yocum et al. clearly show that erythronate 4-phosphate dehydrogenase (PdxB) from E. coli can efficiently produce vitamin B6 in transformed E. coli cells. One of the ordinary skilled in the art would have been motivated to isolate an erythronate 4-phosphate dehydrogenase gene from Sinorhizobium meliloti by searching PdxB homologous gene of Yocum et al. by using BLAST search (global sequence homology search method) wherein the sequence of Capela et al. would have been recognized as a possible erythronate 4-phosphate dehydrogenase gene from Sinorhizobium meliloti, cloning said gene in expression vector and transform the Sinorhizobium meliloti cell for over-producing vitamin B6 by over-producing erythronate 4-phosphate dehydrogenase protein.

It would have been obvious to one to ordinary skill in the art at the time of the invention was made to clone the gene of Capela et al. from Sinorhizobium meliloti, cloning in an expression vector, transform a bacteria or plant cell as taught by Yocum et al. and produce vitamin B6 more efficiently than chemical method as taught by Yocum et al.

Claim 3 is rejected under 35 U.S.C. 103 (a) as being obvious over Capela et al. (UniProt Accession No. Q92RK3, Putative oxidoreductase protein, created 12/1/2001, see IDS), Capela et al. (Analysis of the chromosome sequence of the legume symbiont Sinorhizobium meliloti strain

1021, Proc Natl Acad Sci U S A. 2001 Aug 14; 98(17): 9877-82. Epub 2001 Jul 31, see IDS) in view of Yocum et al. (US PGPUB 2005/0164335 A1, publication 7/28/2005, claim priority of 60/367,863 of 3/25/2002 and 60/368,618 of 3/29/2002) and further in view of Tazoe et al. (Biosynthesis of vitamin B6 in Rhizobium: in vitro synthesis of pyridoxine from 1-deoxy-D-xylulose and 4-hydroxy-L-threonine, Biosci Biotechnol Biochem. 2002 Apr; 66(4): 934-6). Capela et al. (UniProt) teach a putative oxidoreductase protein, which is 100% identical to SEQ ID NO: 2 of the instant application, inherently a erythronate4-phosphate dehydrogenase and the corresponding nucleotide sequence (SMc00985 gene, PNAS 2001), which is 100% identical to the nucleic acid sequence of SEQ ID NO: 1 of the instant application. Capela et al. do not teach a process for producing vitamin B6.

However, Yocum et al. teach a process for producing pyridoxal or pyridoxine or vitamin B6 comprising a host cell, wherein host cell is E. coli, comprising a PdxB gene (pyridoxine or vitamin B6 biosynthetic gene), which is very similar to PdxR gene of instant application, culturing the recombinant host cell, producing vitamin B6 and recovering from the culture. Yocum et al. do not teach use of Sinorhizobium as a transformed host cell for producing vitamin B6.

However, Tazoe et al. teach vitamin B6 over-production in Rhizobium (Sinorhizobium) from 1-deoxy-D-xylulose and 4-hydroxy-L-threonine as substrates. Tazoe et al. also teach an enzyme reaction system with a crude enzyme solution of R. meliloti IFO14782 with NAD+, NADP+, and ATP as coenzymes for biological production of vitamin B6.

It has long been known that Sinorhizobium (Rhizobium) meliloti is an over-producer of vitamin B6 (constitutively). Yocum et al. clearly show that erythronate 4-phosphate

dehydrogenase (PdxB) from E. coli can efficiently produce vitamin B6 in transformed E. coli cells. One of the ordinary skilled in the art would have been motivated to use transformed Sinorhizobium meliloti cell for the production of vitamin B6, which is known to over-produce vitamin B6 as taught by Tazoe et al. by transforming with erythronate4-phosphate dehydrogenase gene of Capela et al. from Sinorhizobium meliloti for producing enhanced amount of vitamin B6 by the method of Yocum et al.

One of ordinary skill in the art would have a reasonable expectation of success because isolating vitamin B6 producing enzyme gene (erythronate 4-phosphate dehydrogenase) from Sinorhizobium meliloti and use the same cell Sinorhizobium meliloti as a host cell for producing vitamin B6 would be advantageous since cellular factors would easily recognize the promoter enhancer region of said gene and over-produce the erythronate 4-phosphate dehydrogenase protein leading to over-production of vitamin B6.

Conclusion

Status of the claims:

Claims 1-3 are pending.

Claims 1-3 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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